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TITLE: Effects of Burn Injuries on Thermoregulatory and Cardiovascular Responses in Soldiers: Implications for the Standards of Medical Fitness

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14. ABSTRACT The aim of this study was to investigate whether the absolute effective body surface area (BSA) or the %BSA burned best predicts the core temperature response to exercise in the heat. Sixteen healthy non-burned individuals [8 large (LG) and 8 small (SM)] were recruited. On separate occasions, subjects cycled at ~100 W for 1 h in a 39°C, 20% relative humidity environment with a simulated burn injury of 0% or 40% total BSA. A simulated 40% burn injury reduced the effective BSA to 1.35±0.05 m <sup>2</sup> and 1.01±0.07 m <sup>2</sup> in LG and SM groups, respectively. Greater elevations in core temperature were observed in SM, irrespective of condition. For both groups, the elevation in core temperature was exacerbated by the 40% simulated burn (P<0.01), yet the magnitude of the increase in core temperature from 0% to 40% simulated burn was not different between groups (P=0.37). Despite the same 40%BSA burned, smaller individuals showed an ~0.75 °C greater elevation in core temperature during exercise. In exercise-based rehabilitation or physically demanding occupational settings, activities performed at the same absolute intensity will place burn survivors of smaller body size, but with the same %BSA burned, at greater risk for hyperthermia.					
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## **1. INTRODUCTION**

The U.S. Army's Standards of Medical Fitness pertaining to a prior burn injury is based upon the findings of only three studies, from a total of 9 subjects with burns of >40% body surface area (BSA; N=4, 3, and 2), and report contradictory findings. Equally low number of subjects were assessed in individuals with <40% BSA burned in those studies. Notably, we know nothing about the interactive effects of differing workload requirements (e.g., metabolic heat generation associated with military service) and the environmental conditions soldiers often operate in on the safety and well-being of a soldier with a prior burn injury. Further, we know nothing about the effects of differing body sizes, location of burn injury, and/or how a soldier's uniform/body armor may affect thermoregulatory and cardiovascular responses during military operations of a soldier with a burn injury. Clearly, there is insufficient information to make conclusions regarding the potential detrimental effects of a prior burn injury at the level necessary to include such recommendations in the Standards of Medical Fitness. The proposed work will provide clear and scientifically-supported guidelines that will culminate in recommendations for a revision of the US Army's Standards of Medical Fitness for burn injuries to more accurately predict the consequences of the injury on the safety and wellbeing of the burned soldier. This information will also have direct impact on the accession/retention of the burned soldier, potentially allowing highly trained, but burned, soldiers to remain in service and thereby realizing cost savings to the Army that would otherwise be spent on training replacements. Finally, the obtained information will benefit the civilian burn community, and those who treat such individuals, through specific recommendations that are dictated in part by the activity level and/or environmental conditions such individuals participate in, with a goal of mitigating the risk of heat-related injuries in this population.

## **2. KEYWORDS**

Army's Standards of Medical Fitness; burn injury; soldier; thermoregulation; sweating; heat dissipation; exercise; metabolic heat generation; environmental climate; temperature; humidity; body surface area burned; donor site; fitness.

## **3. ACCOMPLISHMENTS**

What were the major goals of the project: For year 1 (October 1, 2015 – September 30, 2016) the Statement of Work indicates that we will obtain IRB and HRPO approvals for Aim 1 and we will initiate data collection for protocols 1A and 1B. Aim 1 addresses whether the absolute body surface area for heat dissipation (i.e., m<sup>2</sup> non-injured skin) more accurately predict adverse thermoregulatory and cardiovascular consequences during exercise in hyperthermic conditions relative to the percent body surface area burned? Aim 1A addresses this question in uninjured subjects with simulated burns while Aim 1B addresses this question in burned patients.

What was accomplished under these goals?: We obtained IRB approval from the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas for Aims 1, 2, and 4 of the proposed work. In addition, we successfully navigated the HRPO process and received HRPO approvals for those same aims. With those approvals in hand we initiated data collection for Aim 1A. The protocol in Aim 1A requires 10 small and 10 large subjects to undergo two thermal challenges each, one in which a 40% simulated burn is "caused" and the other in a non-burned state. We are pleased to indicate that to date, 16 subjects have completed that protocol, 8 from each of the two groups. The residual 2 subjects per group are scheduled to be completed before the New Year. Below is the abstract from that work that was submitted for presentation at the American Burn Association meeting in 2017. That abstract outlines the methods and results.

**Introduction:** The excision of burned skin and subsequent grafting typically removes sweat glands, resulting in attenuated heat loss from the grafted area and potentially dangerous elevations in core temperature during physical activities. Although the percentage of body surface area burned (%BSA) is often used to determine the extent of a burn injury, this metric does not account for body size and the absolute non-grafted BSA (in square meters) available for heat loss (the effective BSA), which would be greater in large individuals for a given %BSA burned. Using a simulated burn injury model, the aim of this study was to investigate whether the absolute effective BSA or the %BSA burned best predicts the core temperature response to exercise in the heat. **Methods:** Sixteen healthy non-burned individuals [8 large (LG):  $99.1 \pm 8.4$  kg,  $2.25 \pm 0.09$  m<sup>2</sup>; 8 small (SM):  $62.4 \pm 5.8$  kg,  $1.69 \pm 0.11$  m<sup>2</sup>] were recruited. On separate occasions, subjects cycled at ~100 W for 1 h in a 39°C, 20% relative humidity environment with a simulated burn injury of 0% or 40% total BSA. Burns were simulated using an absorbent material with a vapor-impermeable exterior that prevented sweat evaporation. Changes in core temperature were assessed from gastrointestinal temperature. **Results:** A simulated 40% burn injury reduced the effective BSA to  $1.35 \pm 0.05$  m<sup>2</sup> and  $1.01 \pm 0.07$  m<sup>2</sup> in LG and SM groups, respectively. Greater elevations in core temperature were observed in SM, irrespective of condition (see figure). For both groups, the elevation in core temperature was exacerbated by the 40% simulated burn ( $P < 0.01$ ), yet the magnitude of the increase in core temperature from 0% to 40% simulated burn was not different between groups (LG:  $0.49 \pm 0.24$ °C, SM:  $0.66 \pm 0.41$ °C;  $P = 0.37$ ). **Conclusions:** Despite the same 40%BSA burned, smaller individuals showed an ~0.75 °C greater elevation in core temperature during exercise. However, the intra-individual core temperature augmentation to a 40% simulated burn injury was not dependent on body size.

#### **Applicability of Research to**

**Practice:** In exercise-based rehabilitation or physically demanding occupational settings, activities performed at the same absolute intensity will place burn survivors of smaller body size, but with the same %BSA burned, at greater risk for hyperthermia.

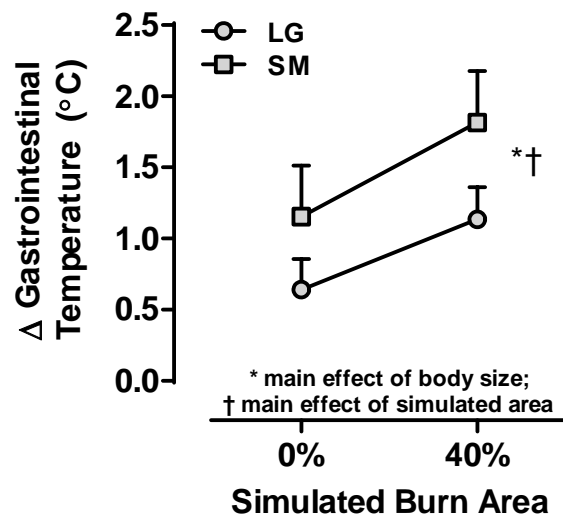


Figure 1: The increase in internal temperature (gastrointestinal temperature) from large (LG) and small (SM) individuals who exercised in a hot climate with 0% and 40% simulated burn injury. These data indicate that despite the identical exercise workload (and thus the identical heat generation), the smaller individuals had a greater elevation in gastrointestinal temperature at both levels of simulated burn.

Aim 1B evaluates the same responses as depicted in Figure 1 but in individuals with an actual burn injury covering ~40% of their body surface area. With that said, we have changed our approach in the recruitment of burned individuals. Given that a large number of the evaluated burned individuals will not live in the Dallas/Fort Worth area, and thus will require long distance travel to our laboratory, we decided to obtain data from protocols 1, 2, and 4 during each of these visits. We are confident this approach will facilitate obtaining the proposed data since rather than three unique visits, only one (somewhat longer) visit will be required for individuals with burn injuries. With that said, we are currently in the process of identifying suitable individuals with burn injuries to obtain the data necessary for Protocol 1B, as well as protocols 2

and 4. Thus, rather than completing data from Protocol 1B in year 2 of the proposal, we will likely take ~3 years to complete data collection for Protocols 1B, 2D and 4. See the Changes/Problems section below where this modification is more thoroughly outlined.

We have also initiated data collection for Aim 2A (evaluates the extent to which a burn injury is detrimental to an individual is dependent on the ambient temperature at a given exercise intensity).

What opportunities for training and professional development has the project provided?:

Though the project was not intended to provide training or professional development opportunities, training has nonetheless taken place as a result of the performed work. Specifically, Matt Cramer, Ph.D. and Gilbert Moralez, Ph.D. are postdoctoral fellows working on this project. As a result of this project, both received training in the following areas: IRB approvals, subject recruitment (both uninjured and burned subjects), data collection and management, data analysis and reporting (see the submitted abstract above), and presentation of the data. Regarding the last point, data from these studies have been presented at weekly “Works in Progress” meetings, and we anticipate the data outlined above will be presented by Dr. Cramer at the American Burn Association meeting in 2017.

How were the results disseminated to communities of interest?: Upon acceptance, the data outlined above will be presented at the 2017 American Burn Association by a postdoctoral fellow working on this project (Matt Cramer, Ph.D.). In addition, components of these data were presented in a seminar given by Dr. Crandall entitled “Thermoregulation in healthy and diseased/injured humans” at the Science of Sport, Exercise and Physical Activity in the Tropics meeting in Townsville, Australia.

What do you plan to do during the next reporting period to accomplish the goals?: In year 2 the statement of work indicates that we will complete data collection for Aim 1A and 1B and we will initiate data collection for Aim 2A and 2C. We have already initiated data collection for Aim 2A. We fully expect to complete data collection for Aim 1A within the next year (likely before Jan 2017). As outlined above, data for Aim 1B will be obtained concurrently with protocols outlined in Aim 2 and 4 from burned individuals, as they are recruited and travel to Dallas to participate in a battery of trials over the course of a 3-4 days. Thus completion of Aim 1B (along with Aims 2D and 4) will require ~3 years. Though this is a slight modification of the statement of work, it will improve efficiency as burned individuals will require only one visit to Dallas to obtain the proposed data.

With that said, during the next reporting period we will i) initiate data collection in a few individual with burn injuries, addressing objectives outlined in Aims 1B, 2D, and 4; ii) continue and likely complete data collection for Aim 2A, which evaluates the extent to which a burn injury is detrimental to an individual is dependent on the ambient temperature at a given exercise intensity. This is a very aggressive protocol, requiring each subject to complete 9 experimental visits, across differing simulated burn coverage and two environmental temperatures; iii) initiate data collection for Aim 2C, which evaluates the effects of the size of the burn injury on an individual’s maximum ability to dissipate heat (*E<sub>max</sub>*).

#### **4. IMPACT**

What was the impact on the development of the principal discipline of the project?:

Given that the project remains in its infancy, the impact of the project remains in the developmental state. That said, information obtained from Aim 1A and outlined above will be valuable to the military and rehabilitations communities. Specifically, the obtained information indicates that the thermoregulatory consequence of a burn injury of a given relative size (e.g.,

40% of total body surface area) is heavily influenced by the overall size of the individual. That is, a smaller individual having the exact same percentage of his/her body surface area burned is at a greater risk for a hyperthermic injury relative to a larger individual having the exact same percent body surface area burned. These data alone are sufficient to question the Army's Standard of Medical Fitness requirement of a single qualifier stating that >40% body surface area burned "does not meet the standard", since if the burned individual is large s/he will be better able to tolerate a hyperthermic insult relative to if s/he were small.

What was the impact on other disciplines?: The obtained data will be of interest to the civilian burn rehabilitation community. Exercise is critical for appropriate rehabilitation. That said, burned individuals are often hesitant to perform aerobic exercise training for fear that they may experience a heat-related injury. The information presented above will be very beneficial to the rehabilitation community by instructing them that a larger person with the same percent body surface area will be better able to "thermally" tolerate exercise at a given rate of metabolic heat generation relative to a smaller person, thereby improving the safety of the rehabilitation of individuals with these injuries.

What was the impact on technology transfer?: Nothing to report.

What was the impact on society beyond science and technology?: Nothing to report.

## **5. CHANGES/PROBLEMS**

Changes in approach and reason for change: We will combine data collection in burned individuals (Aims 1B, 2D, and 4) into a single visit to Dallas. Though we will recruit from the Dallas/Fort Worth area, given the selective nature of the inclusion criteria for burned patients (e.g., having small/large stature with ~40% of their body surface area burned), we recognize that we will also need to recruit nationally to obtain the desired number of subjects, and thus many subjects will need to come from out of town to complete the protocol. It would be inefficient for these individuals to travel to Dallas to complete Aim 1B, and then go home only to return to Dallas in year 3 to complete Aim 2D, and then back to Dallas in Year 4 to complete Aim 4. Thus, when a burned individual is identified and is willing to participate in these protocols, s/he will be asked to complete data collection during one visit spanning 3-4 days. We estimate that using this approach we will complete data collection for Aims 1B, 2D, and 4 in the 4<sup>th</sup> year of the protocol. Please note that this change is merely an "organizational" change, as the data that will be obtained are identical to that previously outlined in the proposal.

Actual or anticipated problems or delays and actions or plans to resolve them: Recruitment of individuals having burn injuries is always challenging, let alone such individuals with fairly narrow inclusion criteria (e.g., large and small individuals having ~40% body surface area burned). That said, we have a clear pathway to identify and recruit these individuals. We have begun with the "low hanging fruit" by recruiting burned individuals who have previously participated in our studies and expressed an interest in continued participation. We also will recruit individuals from the World Burn Congress, which is a national support group meeting for burn survivors and their families/friends. We will have a booth at this meeting to recruit individuals who fall within the inclusion/exclusion guidelines. We are also working with the burn unit at Parkland Hospital and the Department of Surgery at the University of Texas Southwestern Medical Center, both of which maintain a burn injury database that we have begun the process to obtain the necessary permissions to access. Finally, we have communicated with the US Army to inquire about accessing their database of burned

individuals. Though getting that access may be insurmountable, we will continue working to do so.

Changes that had a significant impact on expenditures: None

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: No changes were enacted. The IRB protocols were approved and renewed on 6/15/2016, with an annual expiration date (requiring submission of continuing renewal) of 6/15/2017.

Significant changes in use or care of human subjects: None

Significant changes in use or care of vertebrate animals: None

Significant changes in use or care of biohazards and/or select agents: None

## **6. PRODUCTS**

Publications, conference papers, and presentations:

Journal publications: None

Books or other non-periodical, one-time publications: One abstract has been submitted to the American Burn Association for consideration for presentation at their 2017 national meeting. This abstract would be considered "under review" since we have not received notification of its acceptance for presentation. Yes, that submission cites federal support.

Other publications, conference papers, and presentations: In September 2016 Dr. Crandall gave an oral presentation entitled "Thermoregulation in healthy and diseased/injured humans" at the Science of Sport, Exercise and Physical Activity in the Tropics meeting in Townsville, Australia. Some of the data obtained thus far were presented at that meeting. Moreover, Matt Cramer, Ph.D. has presented data originating from this work twice at our weekly "in house" works in progress events during the prior year.

Website(s) or other Internet site(s): None

Technologies or techniques: None

Inventions, patent applications, and/or licenses: None

Other products: None

## **7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

What individuals have worked on the project?

Name: Dr. Craig Crandall

Project Role: PI

Researcher Identifier:

Nearest person month worked: 4



Contribution to Project: Dr. Crandall has worked extensively with the lab team while planning and implementing data collection and analysis.

Funding Support: Dr. Crandall receives extramural funding from the Department of Defense and the NIH

Name: Matt Cramer, Ph.D.

Project Role: Post-doctoral fellow

Researcher Identifier:

Nearest person month worked: 9

Contribution to Project: Dr. Cramer assists with all aspects of the study, from recruitment through data analysis. This contribution has been quite extensive as each subject requires multiple visits to the laboratory to accomplish the stated aims.

Funding Support: Dr. Cramer receives extramural funding support from grants to Dr. Crandall from the NIH and the Department of Defense.

Name: Gilbert Moralez, Ph.D.

Project Role: Post-doctoral fellow

Researcher Identifier:

Nearest person month worked: 1

Contribution to Project: Dr. Moralez assists with data collection.

Funding Support: Dr. Moralez receives extramural funding support from grants to Dr. Crandall from the NIH and the Department of Defense.

Name: Naomi Kennedy RN, BSN

Project Role: Research Nurse

Researcher Identifier:

Nearest person month worked: 3

Contribution to Project: Naomi has assisted with subject screening and consenting, data collection, and subject safety.

Funding Support: Ms Kennedy receives extramural funding support from grants to Dr. Crandall from the NIH and the Department of Defense

Name: Amy Adams, M.S.

Project Role: Research Associate

Researcher Identifier:

Nearest person month worked: 3

Contribution to Project: Ms Adams assists with subject recruitment, scheduling, and with data collection and reduction.

Funding Support: Ms Adams receives extramural funding support from grant to Dr. Crandall from the NIH and the Department of Defense

Name: Manall Jaffrey, M.S.

Project Role: Research Associate

Researcher Identifier:

Nearest person month worked: 1

Contribution to Project: Ms Jaffrey assists with subject recruitment, scheduling, and assisted with data collection and reduction.

Funding Support: Ms Jaffrey receives extramural funding support from grant to Dr. Crandall from the NIH and the Department of Defense

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?: Yes, two small grants where Dr. Crandall was the PI and a co-investigator ended. 1) A grant from the National Multiple Sclerosis Society ended, which Dr. Crandall (PI) devoted 10% of his time to. 2) A grant from the Department of Defense/American Burn Association ended, which Dr. Crandall (co-investigator) devoted 5% of his time to. The ending of these grants does not impact the support for the present project. No new other support has occurred since the last reporting period.

What other organizations were involved as partners?: Nothing to report.

## **8. SPECIAL REPORTING REQUIREMENTS**

Collaborative Awards: Not applicable

Quad Chart: See attachment

# Effects of Burn Injuries on Thermoregulatory and Cardiovascular Responses in Soldiers: Implications for the Standards of Medical Fitness

BA150093

W81XWH-15-1-0647

PI: Craig Crandall, Ph.D.

Org: Univ of Texas Southwestern Medical Center Award Amount: \$2,017,168

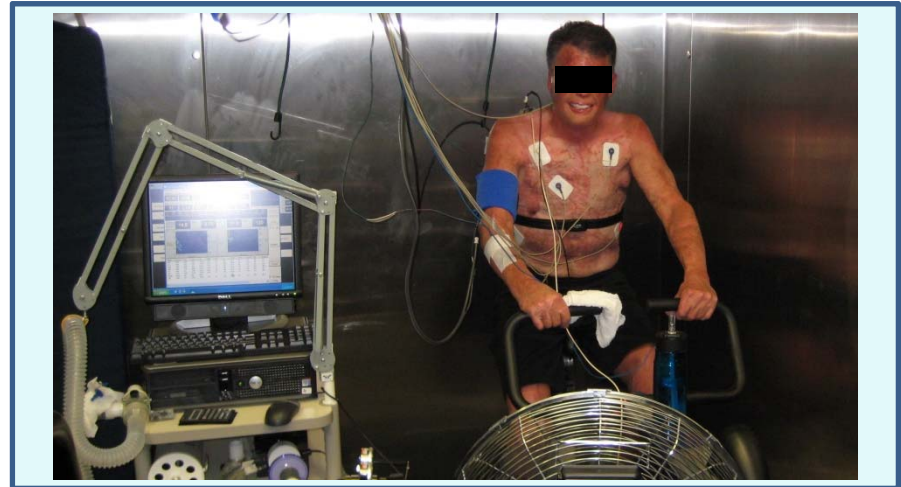


## Study/Product Aim(s)

- Aim 1: Absolute body surface area (BSA) available for heat dissipation (i.e., uninjured skin) more accurately predicts thermoregulatory and cardiovascular consequences during a thermal stress relative to the current standard of using %BSA burned.
- Aim 2: The extent to which a burn injury is detrimental to an individual is dependent on the ambient temperature at a given exercise intensity and the exercise intensity within a given environment.
- Aim 3: Does the location of the burn injury influence thermoregulatory responses?
- Aim 4: Does the donor site contribute to compromised thermoregulatory responses in burned individuals.
- Aim 5: Identification of an upper limit for which a soldier with a prior burn injury could be expected to maintain a safe core body temperature across differing metabolic demands and environmental conditions.

## Approach

The above questions will be addressed primarily by measuring thermoregulatory responses (e.g., core and skin temperatures) during exercise in neutral and hyperthermic environments at various workloads (e.g. rate of metabolic heat generation) in individuals with simulated burn injuries and in actual burn patients.



Accomplishment: We continue to collect data for Aim 1 and have initiated data collection for aim 2. Twenty-six subjects have enrolled with 12 completing the multi-visit protocols.

## Timeline and Cost

Activities	CY	16	17	18	19	20
Aim 1: Body surface area						
Aim 2: Effect of workload and climate						
Aim 3: Burn location						
Aim 4: Donor site						
Aim 5: Compilation						
<b>Estimated Budget (\$K)</b>		<b>\$431</b>	<b>\$375</b>	<b>\$395</b>	<b>\$399</b>	<b>\$419</b>

Updated: 10/10/2016

## Goals/Milestones (Example)

**CY16 Goal** – Obtain IRB and HRPO approvals. Begin data collection close to completion for Aim 1.

**CY17 Goals** – Complete Aim 1A and initiate Aims 1B, 2, and 4

**CY18 Goal** – Continue data collection for Aims 1B, 2, and 4

**CY19 Goal** – Continue data collection for Aims 1B, 2, and 4.

**CY20 Goal** – Complete data collection for Aims 1, 2, 3 and 4. Complete the synthesis of the obtained data and provide guidelines regarding burn injury size/location, environmental condition, and workload by which a burned soldier could safely perform his/her duties (Aim 5).

## Comments/Challenges/Issues/Concerns

- We anticipate completing data collection for Aim 1A within a few months. We have begun data collection for Aim 2A and anticipate its completion in CY17. Data collection in individuals with burn injuries (Aim 1B, 2D, and 4) will occur throughout the funding period (as they are identified) into CY20.

## Budget Expenditure to Date

Projected Expenditure: \$430,982.00

Actual Expenditure: \$266,630.50